American Journal of Hematology 57:225–227 (1998)

Severe Juvenile Vaginal Bleeding Due to Glanzmann's Thrombasthenia: Case Report and Review of the Literature

Ofer Markovitch,[1] Martin Ellis,[2] Michael Holzinger,[3] Shmuel Goldberger,[1] and Yoram Beyth[1]*

[1]Department of Obstetrics and Gynecology, Meir Hospital, Kfar Saba, Israel
[2]Division of Transfusion Medicine, Meir Hospital, Kfar Saba, Israel
[3]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Glanzmann's thrombasthenia is a rare inherited hematological disorder defined by deficiency or abnormality of the glycoprotein (GP) IIb-IIIa complex. Presenting symptoms are hemorrhagic events, mainly epistaxis, purpura, or menorrhagia. We describe the clinical course and management of a 14-year-old girl with Glanzmann's thrombasthenia and severe menorrhagia. Following treatment with 20 U of packed red blood cells, 37 U of platelets, 7 U of fresh frozen plasma, cryoprecipitate, intravenous estrogens, and methylergotrine maleate with no improvement, the uterine cavity was packed for 48 hr. This unusual procedure halted the bleeding and avoided the necessity for a hysterectomy. When treating acute menorrhagia in patients with Glanzmann's thrombasthenia, the physician should be familiar with the characteristics and all treatment modalities for this disorder. Am. J. Hematol. 57:225–227, 1998. © 1998 Wiley-Liss, Inc.

Key words: Glanzmann's; thrombasthenia; juvenile; menorrhagia

INTRODUCTION

Glanzmann's thrombasthenia is a rare autosomal recessive disorder of platelet function that is characterized by deficiency or abnormality of the membrane glycoprotein IIb-IIIa complex [1–10]. The laboratory criteria for diagnosis of this disorder include normal platelet count, normal platelet morphology, prolonged bleeding time, absent or severely diminished platelet aggregation in response to adenosine diphosphate and other agonists, normal platelet agglutination by ristocetin, and normal plasma coagulation studies [11]. The clinical presentation includes hemorrhagic symptoms, mainly purpura, epitaxis, gingival hemorrhage, and menorrhagia [11]. The severity of bleeding in thrombasthenia is unpredictable: some patients may require multiple red blood cell transfusions, while others may not manifest evidence of bleeding. Acute juvenile vaginal bleeding is one of the important clinical manifestations of this disorder which sometimes necessitates aggressive and even invasive treatment.

CASE REPORT

A 14-year-old girl was admitted to the Gynecology Department due to heavy menstrual bleeding. She was known to have Glanzmann's thrombasthenia and had been hospitalized in the past due to nasal bleeding, which required blood transfusions. Of her five siblings, one sister and one brother suffered from the same disorder. The brother was asymptomatic, whereas the sister displayed acute menorrhagia during her first menstrual period but did not require any intervention.

The patient's first menstrual period, lasting 9 days with heavy bleeding, occurred 3 months prior to admission. The second menstrual period began 2 weeks before hospitalization and lasted until the day of her admission. The bleeding gradually worsened and the patient noted blood clots during the 2 days prior to admission.

*Correspondence to: Yoram Beyth, MD, Department of Obstetrics and Gynecology, Meir Hospital, Kfar Saba, Israel.

Received for publication 16 January 1997; Accepted 9 July 1997

Physical examination revealed no abnormalities. Gynecological examination by speculum showed moderate bleeding. Laboratory findings included a hemoglobin of 6.6 g/dl and reticulocytosis with no evidence of hemolysis. Platelet count, prothrombin time (PT), and partial thromboplastin time (PTT) were normal. The bleeding time performed by the Ivy method was 17 min (normal = 2.9 min). An abdominal ultrasound scan revealed hematocolpus of 50–80 ml.

The patient received 6 U of packed red blood cells. Treatment with conjugated estrogen tablets 1.25 mg three times daily and oral Tranexamic acid 500 mg three times daily was instituted. Vaginal bleeding, estimated by pad collection, was moderate. The vaginal bleeding did not subside and on the 4th day of hospitalization, the patient's hemoglobin dropped to 3.6 g/dl. Her platelet count was 97,000/μl and the PT and PTT were normal.

Abdominal ultrasound showed hematocolpus and hematometra. Computed tomography of the abdomen was normal. Profuse vaginal bleeding continued, requiring treatment with packed red blood cell transfusions (14 U), fresh frozen plasma (7 U), and platelets (37 U). Intravenous conjugated estrogen methylergotrine maleate and Tranexamic acid were administered.

Examination under general anesthesia was performed, and fresh blood was seen emanating from the uterine cavity. Two uterine tampons were inserted and were able to tamponade the bleeding. The intrauterine tampons were removed 48 hr later and no active bleeding was evident.

The patient was discharged several days later after receiving an oral contraceptive and an iron compound.

DISCUSSION

A primary coagulation disorder accounts for 20% of acute adolescent menorrhagia [12]. These coagulation disorders include mainly idiopathic thromocytopenia purpura (ITP), von Willebrand's disease, and thrombasthenia. In contrast to the first two disorders, clinical reports of thrombasthenia and juvenile vaginal bleeding are rare.

Thrombasthenia was first described by Glanzmann in 1918 as ''hereditary hemorrhagic thrombasthenia'' and includes platelet abnormalities with defective clot retraction and abnormal clot appearance on stained films [13].

This rare disorder is relatively frequent among 4 populations worldwide: French gypsies, Iraqi Jews in Israel, Indians, and Jordanian Arabs [14,15]. This uneven distribution of the disorder is a result of intramarriage in these regions leading to greater expression of autosomal recessive traits.

The pathogenesis of Glanzmann's thrombasthenia is defective platelet hemostatic plug formation, due to deficiency or abnormality of platelet membrane GP IIb-IIIa [5]. These glycoproteins form calcium-dependent complexes that change conformation upon activation and allow fibrinogen binding, which is required for platelet aggregation. Patients with severe GP IIb and IIIa deficiency (less than 5% of normal) are designated type I, patients with moderate deficiency (10–20% of normal) are designated type II. Patients whose primary defect appears to be in the receptor function of GP IIb-IIIa, rather than manifesting as a deficiency, are designated as variants. There is no correlation between the number of GP IIb-IIIa receptors present on the platelet membrane and the severity of hemorrhagic disease [11]. The molecular basis of Glanzmann's thrombasthenia in a variety of population groups has been elucidated [16–18]. The patient described in this report is a member of an Israeli Arab kindred that has been well studied [12]. In this patient, the defect in platelet function has been shown to arise from a 13 base pair deletion in the GP IIb gene at the beginning of exon 4. This defect results in the deletion of six amino acids from the mature protein that is detectable in the patient's platelets using immunoblot analysis. However, no platelet surface GP IIb-IIIa is detectable, suggesting that the deleted amino acids are necessary for post-translational processing of the GP IIb protein and its coupling with GP IIIa. In Iraqi Jews studied, deletions in the genes encoding both GPIIb and IIIa have been detected [19].

The pattern of blood loss in Glanzmann's thrombasthenia is usually one of excessive menstrual bleeding or major bleeding secondary only to minor trauma. Spontaneous bleeding is rare. Most patients are diagnosed before the age of 5 years, either at birth or during early infancy. Bleeding at menarche is a frequent serious problem and it requires blood transfusion in most cases [20]. This may be a result of prolonged estrogen stimulation of anovulatory cycles, causing continuous endometrial proliferation, which in turn results in breakthrough bleeding during menarche [21].

Management of menorrhagia due to thrombasthenia consists of supportive care in addition to hormonal therapy [11,21]. Supportive care includes predominantly blood product administration and hematinics. Adjuvant therapy with high-dose conjugated estrogens administered intravenously for 24–48 hr, followed by high doses of a combined oestrogen-progestin oral preparation, is important in the attainment of hemostasis. At the conclusion of this intense hormonal therapy, continuous treatment with a combined oral contraceptive is recommended for 2–3 months [21]. When the oral contraceptive course ends, the patient is re-evaluated. If the high-dose hormonal management proves to be inadequate and menorrhagia continues, examination under anesthesia (EUA) with dilatation and curettage is a mandatory procedure [21]. The EUA serves as a diagnostic modality to

rule out other pathologic conditions that could potentially cause vaginal bleeding (e.g., foreign body, vaginal tears, benign or malignant cervical tumors) and as a therapeutic procedure. In our patient, bleeding continued during the curettage and decreased dramatically only following packing of the uterine cavity for 48 hr.

Pregnancy and delivery is another potentially dangerous period for women with thrombasthenia [11]. In a series of 21 pregnant women, there was only one case of severe vaginal bleeding that required transfusion. Severe hemorrhage occurred in 6 of 19 deliveries during which platelet concentrates were not transfused. The remaining 13 patients received platelet transfusions and delivered without excessive bleeding. Patients who delivered by Cesarean section had fewer hemorrhagic complications [11]. Since the type of thrombasthenia does not predict the degree of bleeding that is encountered clinically, prophylactic platelet transfusion prior to delivery or invasive procedures generally should be considered in thrombasthenics that have a personal or family history of moderate to severe bleeding.

The prognosis of patients with thrombasthenia is excellent. Although bleeding events may be severe and life-threatening, supportive treatment, prevention of possible bleeding crises, and correction of anemia overcome these problems. On follow-up of 15 Parisian patients, described 23 years ago, only one died of hemorrhage [1]. Other reports of fatal hemorrhagic events are very rare, and there is no documented evidence of death due to menorrhagia associated with thrombasthenia.

We conclude that although thrombasthenia is a rare cause of menorrhagia, it should be considered in the differential diagnosis of young women presenting with abnormally heavy menstrual bleeding. The diagnosis is confirmed by demonstrating the typical findings on platelet aggregation studies. Conservative treatment should be followed by an invasive procedure if menorrhagia continues. However, before hysterectomy is performed in young women, packing of the uterus should be attempted.

REFERENCES

1. Caen JP, Castaldi PA, Leclerc JC, et al: Congenital bleeding disorders with long bleeding time and normal platelet count. I. Glanzmann's thrombasthenia. Am J Med 41:4–26, 1966.
2. Friedman LL, Bowie EJW, et al: Familial Glanzmann's thrombasthenia. Mayo Clin Proc 39:908–913, 1964.
3. Nurden AT, Caen JP: An abnormal platelet glycoprotein pattern in three cases of Glanzmann's thrombasthenia. Br J Haematol 28:253–260, 1974.
4. Bellucci S, Tobelem G, Caen JP: Inherited platelet disorders. Prog Hematol 13:223–263, 1983.
5. George JN, Nurden AT, Phillips DR: Molecular defects in interactions of platelets with the vessel wall. New Engl J Med 311:1084–1098, 1984.
6. Zucker MB, Pert JH, et al: Platelet function in a patient with thrombasthenia. Blood 28:524–534, 1966.
7. Brown CH III, Weisberg RJ, et al: Glanzmann's thrombasthenia: Assessment of the response to platelet transfusions. Transfusion 15:124–131, 1975.
8. Reichert N, Seligsohn U, et al: Clinical and genetic studies of Glanzmann's thrombasthenia in Israel. Thromb Diath Hemorrh 34:806–820, 1975.
9. Khabduri U, Pulimood R, et al: Glanzmann's thrombasthenia: A review and report of 42 cases from South India. Thromb Haemost 46: 717–721, 1981.
10. Nurden AT, Fournier D, Picard D: Pathological aspects of platelet aggregation. A consideration of the heterogeneity in Glanzmann's thrombasthenia. In Marguerie G, Zwaal RFA (eds): ''Biochemistry and Physiopathology of Platelet Membranes.'' London: Libbey, pp 95–96, 1988.
11. George JN, Caen JP, Nurden AT: Glanzmann's thrombasthenia: The spectrum of clinical disease. Blood 75:1383–1395, 1990.
12. Claessens EA, Cowell CA: Acute adolescent menorrhagia. Am J Obstet Gynecol 139:277–280, 1981.
13. Walsh PN: Platelet coagulant activities in thrombasthenia. J Haematol 23:553–569, 1972.
14. Seligsohn U, Rosophansky S: A Glanzmann's thrombasthenia cluster among Iraqi Jews in Israel. Thromb Haemost 52:230–231, 1984.
15. Awidi AS: Increased incidence of Glanzmann's thrombasthenia in Jordan compared with Scandinavia. Scand J Haematol 30:218–222, 1983.
16. Burk CD, Newman PJ, Lyman S, Gill J, Coller BJ, Ponca M: A deletion in the gene for glycoprotein IIb associated with Glanzmann thrombasthenia. J Clin Hematol 87:270–276, 1991.
17. Clemetson KJ, Clemtson JM: Molecular abnormalities in Glanzmann's thrombasthenia, Bernard Soulier syndrome and platelet-type von Willebrand's disease. Clin Opin Hematol 1:388–393, 1994.
18. Jung SM, Yoshida JN, et al: Thrombasthenia with abnormal platelet membrane glycoprotein IIb of different molecular weight. Blood 71: 915–922, 1988.
19. Newman PT, Seligsohn U, Lyman S, Coller BS: The molecular genetic basis of Glanzmann's thrombasthenia in the Iraqi-Jewish and Arab populations in Israel. Proc Natl Acad Sci USA 88:3160–3164, 1991.
20. Hardisty RM, Dormandy KM, et al: Thrombasthenia: Studies on three cases. Br J Haematol 10:371–387, 1964.
21. Speroff L, Glass RH, Kase NG: ''Clinical Gynecologic Endocrinology,'' 5th ed. Baltimore: Williams and Wilkins, p 536, 1994.